The Transepidermal Oxygen Flux from the Environment is in Balance with the Capillary Oxygen Supply

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It has been known since the nineteenth century that oxygen is taken up by the human skin. With a newly developed sensor it became possible to examine the influence of the vascular supply on the oxygen flux into the skin, tcJ(O_2). tcJ(O_2) was measured optically by determining the oxygen partial pressure difference, ΔpO_2 across a diffusion test membrane, which itself was brought into close contact to the skin surface. Under these conditions ΔpO_2 is proportional to the tcJ(O_2). The skin perfusion was varied by the application of a hyperemizing ointment on the abdomen of 12 volunteers and by suprasystolic occlusion at the thigh of 20 volunteers. The tcJ(O_2) was measured at a temperature of 33°C of the humid skin. It was compared with the skin perfusion monitored by laser Doppler flow, and the capillary oxygen supply measured by transcutaneous partial pressure of oxygen, tcpO_2, at an electrode temperature of 37°C. The transcutaneous O_2 flux produced a distinct ΔpO_2 of 81.8 ± 8.2 Torr (abdomen) and 72.8 ± 12.3 Torr (ankle). In hyperemic skin on the abdomen the O_2 flux was reduced (ΔpO_2 = 57.7 ± 10.6 Torr). The tcpO_2 increased from 8.7 ± 10.7 to 35.1 ± 16.9 Torr. During suprasystolic occlusion, ΔpO_2 increased by 6.4 ± 2.3 Torr, whereas laser Doppler flow and tcpO_2 decreased significantly. These results indicate that the total oxygen supply of the epidermis and the upper dermis is guaranteed even if the perfusion varies. ***Key words: laser Doppler flow/microcirculation/optode/skin oxygen supply. J Invest Dermatol 114:533–540, 2000***

Human skin directly takes up O_2 from the atmosphere. In the nineteenth century Gerlach (1851) proved this by fixing a varnished horse bladder filled with clean air on to the skin of his chest and measuring the decrease of O_2 and increase of carbon dioxide 24 h later. This phenomenon is known as "skin respiration". In an atmosphere of air and under resting conditions humans take up between 80 and 100 ml O_2 per m^2 per h through the skin surface (equals roughly 1–2% of the total O_2 requirement) and eliminate 90–120 ml carbon dioxide per m^2 per h (for a review see Fitzgerald, 1957). For the organism as a whole this seems to be of little importance. For the epidermis and the upper dermis, however, the O_2 supply of the skin from the atmosphere plays a quantitative role. This was shown by polarographic measurements of the local O_2 partial pressure, pO_2, within the skin with needle electrodes which were inserted perpendicularly into the skin (**Fig 1**; Baumgärtl *et al*, 1987). Owing to the experimental conditions, the skin surface pO_2 was considerably lower than the atmospheric value (78 Torr instead of 159 Torr). Furthermore, a hyperemia induced by the needle puncture has to be considered. The experiment proved that even under these conditions the upper layers of the skin are supplied by the O_2 of the atmosphere and not by the O_2 of the blood: The pO_2 decreases continuously from a maximum at the surface of the skin until reaching a minimum in the papillary dermis before increasing again under the influence of the vascular supply of O_2 in deeper layers. As the O_2 transport within the tissue occurs

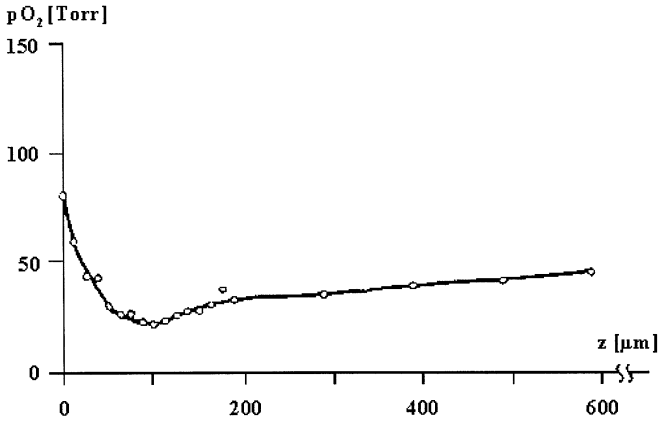

Figure 1. The pO_2 decreases from the skin surface to a minimum at a depth of 100 µm. pO_2 measured by a needle electrode, inserted perpendicularly into the skin. The depth z of the electrode is given in µm (skin surface at 0 µm). The skin surface was covered by a water film, resulting in a reduced skin surface pO_2 of 78 Torr. The pO_2 profile has a distinct minimum at a depth of ≈100 µm, roughly at the level of the dermoepidermal junction (according to Baumgärtl *et al*, 1987). The needle puncture probably resulted in hyperemia. Under more physiologic conditions, the minimum has to be expected at a greater depth.

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Abbreviations: AU, arbitrary unit; pO_2, oxygen partial pressure; tcJ(O_2), transcutaneous oxygen flux into the skin; tcpO_2, transcutaneous partial pressure of oxygen.

along the pO_2 gradient from higher to lower pO_2 values, the whole volume above this minimum is supplied by external O_2.

The transepidermal O_2 flux $tcJ(O_2)$ is increasing proportionally to the increase of the pO_2 gradient between the skin surface and the upper dermis. To measure the $tcJ(O_2)$, Lübbers (1992b) proposed to place an O_2-permeable test membrane, with known diffusion properties, on to the skin surface. As the O_2 flux through the membrane is the same as the flux into the skin, the $tcJ(O_2)$ can be obtained by measuring the pO_2 gradient across that test membrane. This can be performed by optical O_2 sensors, consisting of O_2-permeable silicone layers which contain a luminescence indicator (Lübbers and Karpf, 1995). They can be made very thin and highly O_2 permeable so that their diffusion resistance to O_2 is negligible. They have a further advantage over Clark electrodes as they do not consume O_2 (Lübbers and Opitz, 1975; Opitz and Lübbers, 1987; Lübbers, 1992a). A measuring system with such an O_2 flux optode was constructed by Holst (1994; Holst *et al*, 1995).

In this study the question was examined whether the O_2 flux into the skin is influenced by the cutaneous blood flow. The perfusion of the skin was measured by assessing the laser Doppler flow (Watkins and Holloway, 1978) and the amount of the hematogenic O_2 supply by monitoring the transcutaneous O_2 partial pressure ($tcpO_2$) with a Clark electrode (Huch *et al*, 1981).

MATERIALS AND METHODS

O_2 fluxmetry We used a newly developed prototype to measure the transcutaneous O_2 flux, $tcJ(O_2)$. The measurement set-up is explained in the following.

Optical measurement of the pO_2 The O_2 concentration in the O_2 optode can be measured by dynamic luminescence quenching, i.e., by decreasing intensity or duration of light emission (decay time) of a luminophore by a so-called quencher (Stern and Volmer, 1919). Molecular O_2 is a good quencher of fluorescence and phosphorescence (Kautsky and de Bruijn, 1931; Kautsky, 1939). Suitable, reversible luminophores are ruthenium complexes (Wolfbeis *et al*, 1986). Compared with the intensity, the decay time (lifetime) is the more stable signal and, furthermore, independent of the concentration of the indicator. Therefore this parameter was used. When the intensity of the exciting light is modulated harmonically, the fluorescence intensity shows a phase shift $\Delta\Phi$ depending on the actual decay time, which is determined by the O_2 concentration. The calibration curve is nonlinear and can be described by eqn 1 (Holst, 1994):

$$\Delta\Phi = A \cdot (1 + C \cdot pO_2)/(1 + B \cdot pO_2) \quad (1)$$

The O_2 flux optode was calibrated daily by exposing the optode to water saturated N_2/O_2 gas mixtures with varying O_2 contents (0, 5, 9, 12, 15, 18, 20, and 20.95%). The corresponding pO_2 values were calculated taking into account the actual atmospheric pressure and the temperature dependent partial pressure of H_2O. A, B, and C were determined by a least square fit (Sigma Plot 2.01, Jandel Scientific, Erkrath, Germany). These parameters proved to be strongly dependent on temperature. Therefore, the temperature of the sensor head was kept constant with a tolerance of less than 0.1°C.

Flux sensor The O_2 flux sensor consists of the diffusion test membrane (PFA 50 μm, Nowofol, Siegsdorf, Germany), the underlying O_2 sensor membrane (70 μm thick silicone layer with Tris(2,2-bipyridyl) ruthenium (II) chloride hexahydrate (Strem Chemicals, Kehl, Germany) adsorbed at silica gel particles) and the optical insulation (black silicone, 70 μm). The optical insulation eliminates the fluorescence of the skin (Fig 2). All three layers are permeable to O_2, the two mentioned first are transparent.

During the measurements the lower side of the sensor foil is in contact with the skin surface and measures the pO_2 below the diffusion test membrane (skin surface pO_2). The pO_2 above the diffusion test membrane usually equals the atmospheric pO_2, but the measuring heads allow to apply an artificial atmosphere at the external side of the flux sensor (Fig 2, chamber k) for test purposes. During the experiment, the pO_2 at the skin surface was continuously monitored. The atmospheric pO_2 was recorded before application and after removal of the optode. The difference between the atmospheric and the skin surface pO_2 equals the pressure gradient across the diffusion test membrane, ΔpO_2. The $tcJ(O_2)$ can be calculated as follows:

$$tcJ(O_2) = P \cdot \Delta pO_2 \text{ with } P = K/d \quad (2)$$

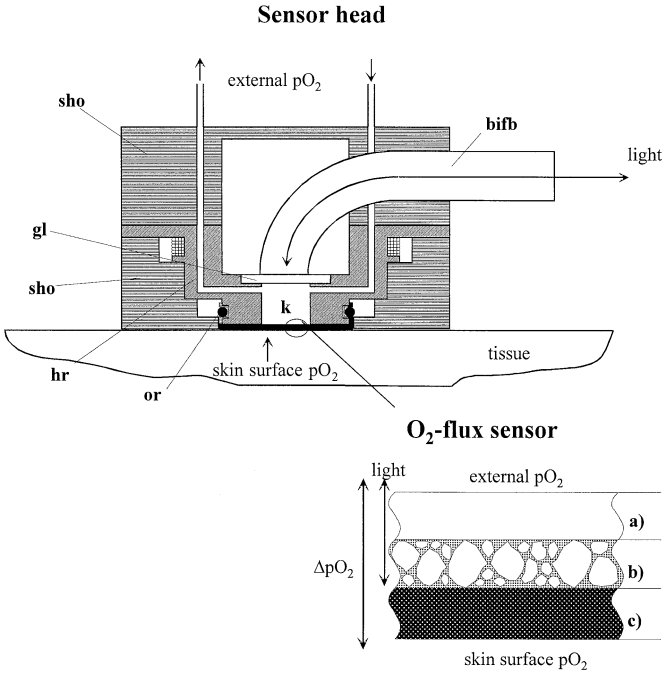

Figure 2. Cross-sections of the $tcJ(O_2)$-measuring head and the sensor membranes. Measuring head: hr, heating ring; gl, glass sealing; sho, sensor housing; k, test chamber with gas supply; bifb, bidirectional fiber optic; or, sealing ring. Sensor membranes: (*a*) diffusion test membrane (PFA); (*b*) O_2 sensor: silicone membrane with silica gel particles to which ruthenium complexes are adsorbed electrostatically; (*c*) optical insulation (black silicone) (according to Holst, 1994).

P denotes the O_2 permeability of the membrane as quotient of its O_2 conductivity K and its thickness d. K is the product of the diffusion coefficient D and the solubility coefficient α of the diffusion test membrane. As the diffusion properties are not altered during the measurement, changes of the $tcJ(O_2)$ can be measured solely by determination of ΔpO_2. In our set-up it is spatially averaged in a circular area with a diameter of 4 mm.

Transcutaneous pO_2 measurement The $tcpO_2$ was measured with an airtight sealed Clark electrode adjusted to 37°C (TCM 3, TINA, Radiometer, Copenhagen, Denmark) (Huch *et al*, 1981). Measurements were recorded with custom-made software.

Laser Doppler flowmetry Laser Doppler flow measurements were carried out at a wavelength of 780 nm (DRT 4, Moor Instruments, Millwey, Axminster, U.K.). Data were recorded with the original software (DRTSOFT, Moor Instruments). The laser Doppler heads contain a temperature sensor. In our experiments the skin temperature varied between 31 and 34°C.

Experimental design We examined 32 healthy volunteers, who by clinical history and physical examination had no vascular diseases, such as peripheral arterial occlusive disease or chronic venous insufficiency. Further exclusion criteria were arterial hypertension, diabetes mellitus, atopic dermatitis, and skin diseases in the examined area. Informed consent was obtained from the participants. The study protocol was reviewed and approved by the Ethics Committee of the Ruhr University Bochum and was conducted in accordance with the Helsinki guidelines.

At a room temperature of 22°C to 23°C the volunteers were acclimatized for 20–25 min lying in a comfortable position with a slightly raised upper body. Prior to application of the probe, the skin to be examined was shaved if necessary and cleaned with 63% propanol (Cutasept, Bode Chemie, Hamburg, Germany). The superficial horny scales were eliminated by stripping 10× with an adhesive tape. At the beginning and in the end of the experiment the signal of the $tcJ(O_2)$ probe was recorded as reference value at normal atmospheric pO_2. After humidifying the skin of the measuring area by applying 50 μl water, the measuring heads were fixed with adhesive rings. The temperature of the sensor head was adjusted to 33°C; the skin surface was in close contact to the heating ring (Fig 2).

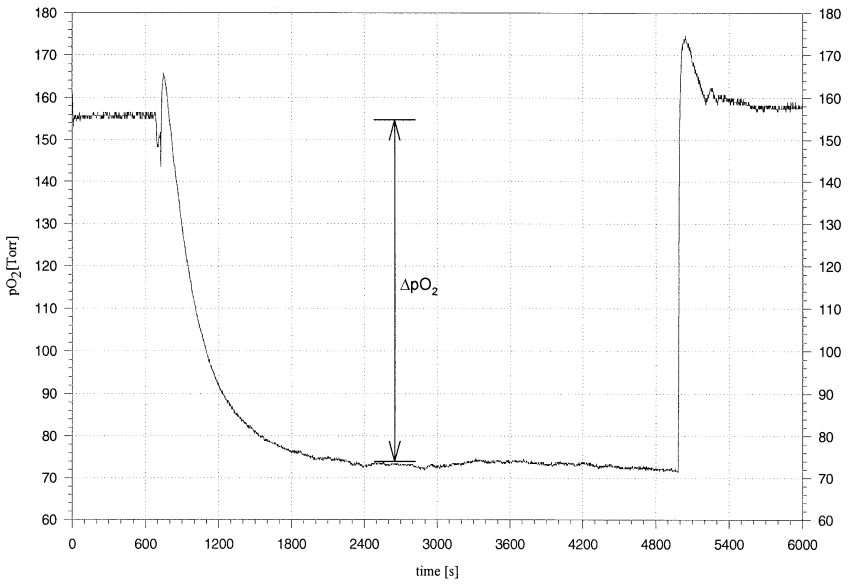

Figure 3. Typical measurement of tcJ(O_2). Measurement of the tcJ(O_2) (33°C) on the skin of the abdomen (untreated reference area, application of the optode at t = 700 s, removal at t = 5000 s). The skin surface pO_2 decreased within 1600 s after fixing the optode to a stable value, which corresponded to a ΔpO_2 of 83.6 Torr across the diffusion test membrane. The atmospheric pO_2 values determined before application and after removal of the optode were 155.7 Torr and 157.7 Torr.

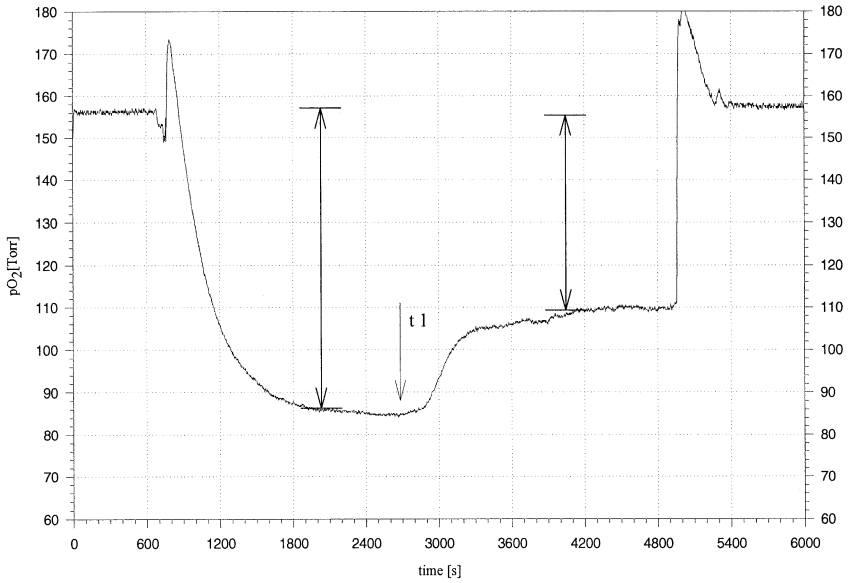

Figure 4. During hyperemia the tcJ(O_2) was reduced. tcJ(O_2) in the test area on the abdomen (same experiment as **Fig 3**). Marked decrease of the ΔpO_2 after application of the ointment at t1 (Change of ΔpO_2 from 70.9 Torr to 47.4 Torr). The atmospheric pO_2 values determined before application and after removal of the optode were 156.1 Torr and 157.5 Torr.

Hyperemizing ointment In 12 healthy volunteers (group A: seven men, five women, age 36 ± 13 y) the tcJ(O_2) and tcpO_2 sensors were placed next to each other in a test area on the skin of the abdomen. A second tcJ(O_2) sensor was placed in a reference area 20 cm distant to the first sensor. After recording stable resting values, 0.1 ml of a hyperemizing ointment (nonivamide and nicoboxil ointment, Finalgon Salbe extra stark, Thomae, Biberach an der Riss, Germany) was applied next to the tcpO_2 and tcJ(O_2) sensors in the test area. The distance between the treated skin surface and the sensitive area of the probes amounted to 10 mm (tcpO_2) and 13 mm [tcJ(O_2)]. Reactions were recorded for 20 min. Owing to the limited homogeneously hyperemic area, laser Doppler measurement was not carried out.

Suprasystolic occlusion In 20 volunteers (group B: 16 females, four males, mean age 37 ± 13 y) the tcJ(O_2) sensor and the laser Doppler probe were placed next to each other 10 cm proximal to the medial ankle. The tcpO_2 measuring head (temperature 37°C) was placed 15 cm proximal to the medial ankle. In order to receive a defined change of skin perfusion after the resting values were obtained, a 5 min suprasystolic arterial occlusion with a blood pressure cuff applied to the thigh was performed. After opening the cuff, the measurement was continued until stable values were obtained again.

Statistical analysis Using repeated measures analysis of variance and the t test for paired samples we tested the data for significant differences. Significance was set at $p \leq 0.05$ (SAS 6.12, SAS Institute, Cary, NC). Data are presented as mean ± standard deviation.

RESULTS

Test of the O_2 flux sensor

Reproducibility Stability of the optodes was tested by three calibration cycles within 9 h. The fit parameters of eqn 1 were determined in the first cycle. In the second and third cycle, the mean absolute deviations from the nominal pO_2 values were 0.04 Torr and 0.06 Torr, the maximum deviations were 0.1 Torr and 0.2 Torr. During the experiments, the stability was controlled by comparing the calculated pO_2 values before application and after removal of the optode. Under these conditions a lower accuracy was observed (see **Figs 3**, **4**, and **8**). All measurements included in this study showed a difference of less than 5 Torr.

Response time To characterize the dynamic behavior of the O_2 flux sensor, the time course of the skin surface pO_2 after application of the optode was examined (**Fig 8**). At the localization 10 cm proximal to the medial ankle, 90% of the final ΔpO_2 was reached on average within 24 ± 6 min. If in contrast the optode was exposed to a change of the composition of the surrounding gas

Table I. tcJ(O_2) at 33°C (ΔpO_2) and tcpO_2 at 37°C before, during and after application of a hyperemizing ointment, determined on the skin of the abdomen (group A). Additionally, ΔpO_2 was recorded in an untreated reference area before (1) and after (2) application of the ointment in the test area

Volunteer	Age (y)	ΔpO_2 at rest (Torr)	ΔpO_2 hyperemia (Torr)	ΔpO_2 reference 1 (Torr)	ΔpO_2 reference 2 (Torr)	tcpO_2 at rest (Torr)	tcpO_2 hyperemia (Torr)
1	24	80.7	53.4	63.8	65.8	18.8	27.3
2	39	72.6	43.5	62.7	65.7	9.2	15.4
3	38	87.9	70.6	72.5	71.9	1.3	54.2
4	33	82.8	47.6	74.3	75.2	6.3	72.4
5	17	66.5	50.5	63.8	65.1	38.4	40
6	29	78.4	56.3	73.5	75.3	1.3	6.7
7	67	71.4	46.3	82.5	83.6	3.7	35.9
8	44	83.9	55.9	83.8	87	2.5	41.6
9	28	84.2	63.4	89.9	84	2.2	30.6
10	55	88.5	56.7	79.3	82.1	1.7	46.5
11	31	97.2	81.3	90.1	92	16.7	29.3
12	26	87.6	67.2	92.1	94.9	1.9	21.7
Mean	35.9	81.8	57.7	77.4	78.6	8.7	35.1
SD	14.0	8.5	11.1	10.6	10.3	11.1	17.7

Table II. tcJ(O_2) at 33°C (ΔpO_2), laser Doppler flow at 31–34°C (LDF) and tcpO_2 at 37°C before, during and after a suprasystolic occlusion (hyperemia), determined 10 cm proximal to the medial ankle (group B)

Volunteer	Age (y)	ΔpO_2 at rest (Torr)	ΔpO_2 occlusion (Torr)	ΔpO_2 hyperemia (Torr)	LDF at rest (AU)	LDF occlusion (AU)	LDF hyperemia (AU)	tcpO_2 at rest (Torr)	tcpO_2 occlusion (Torr)	tcpO_2 hyperemia (Torr)
1	50	46.6	52.0	47.2	20.2	11.7	43.0	10.0	5.4	19.6
2	19	81.8	91.6	81.2	24.7	11.5	35.7	1.8	0.5	9.4
3	46	67.1	76.3	67.1	15.0	11.5	38.6	22.9	7.6	26.9
4	35	59.2	63.6	57.4	33.2	19.3	101.7	32.3	3.1	49.6
5	35	88.8	99.1	92.1	13.6	11.3	34.6	18.6	1.0	20.9
6	23	82.9	90.0	83.0	26.6	16.4	66.6	1.2	0.7	21.4
7	26	78.0	83.2	75.1	21.3	12.4	108.0	3.6	1.5	34.4
8	42	59.0	67.1	56.8	12.2	14.1	62.4	23.0	4.3	30.2
9	35	58.2	64.6	56.2	28.1	10.3	57.6	5.3	1.0	19.5
10	55	57.3	67.7	54.7	21.1	10.8	38.5	9.3	0.8	23.0
11	28	80.0	87.6	77.9	21.0	12.8	44.5	2.7	1.3	17.5
12	24	69.0	75.3	70.3	16.8	17.7	31.5	3.4	1.1	27.7
13	51	93.6	97.8	95.2	12.8	10.3	34.3	3.7	0.8	11.5
14	21	83.1	86.8	81.7	15.7	12.8	48.1	1.1	1.1	13.7
15	46	77.0	83.0	77.8	14.3	12.6	43.8	5.9	1.7	16.6
16	34	70.5	74.7	69.5	33.6	22.1	112.8	11.3	0.8	25.4
17	33	80.6	87.8	81.8	30.1	12.8	88.7	20.3	0.9	27.5
18	18	64.8	69.4	65.6	22.1	9.8	54.4	6.7	0.7	25.5
19	55	76.2	82.1	77.1	27.1	13.5	76.2	5.0	0.7	31.0
20	56	81.5	84.2	81.8	31.6	16.4	84.5	26.9	5.9	30.4
Mean	36.6	72.8	79.20	72.5	22.1	13.5	60.3	10.8	2.1	24.1
SD	12.8	12.3	12.34	13.0	7.0	3.3	26.3	9.6	2.1	9.1

mixture, the signal reaches the corresponding steady state in less than 5 min (Schulze, 1997).

Airtight mounting of the sensor heads Direct entry of atmospheric O_2 into the sensor layer of the optode would result in an underestimation of the ΔpO_2 and consequently of the tcJ(O_2). To rule out such an error, experiments were carried out on two volunteers at the lower leg. Fifty minutes and 70 min after mounting the optode, a stable ΔpO_2 of 66 Torr and 78 Torr was observed. Application of 100% nitrogen on the external side of the flux sensor (**Fig 2**, chamber k) resulted in a reduction of the skin surface pO_2 to 1.4 Torr and 3.4 Torr. Therefore, a marked cross-diffusion of O_2 (e.g., below the adhesive rings) could be ruled out.

Case example In **Fig 3** a typical course of the tcJ(O_2) measurement is shown. Within 27 min of application of the sensor on to the abdomen, the skin surface pO_2 decreased and reached a steady state of 73.1 Torr. After exposing the O_2 flux optode to the normal atmospheric pO_2 again, a value was measured which differed by 2.0 Torr from the pO_2 recorded at the beginning of the experiment. Therefore, a shift of the optode sensitivity which would result in a greater difference can be excluded.

Measurements under normal conditions After application of the optode on the humid skin of the abdomen (group A, **Table I**), the skin surface pO_2 below the optode fell from the atmospheric pO_2 to a considerably lower value. On average, the resulting difference of the partial pressure across the O_2 flux optode amounted to 81.8 ± 8.5 Torr. At the ankle of volunteers of group B (**Table II**), the transepidermal O_2 flux (ΔpO_2) was significantly lower (72.8 ± 12.3 Torr, $p \leq 0.05$). There were no significant regional differences of the tcpO_2 between the two groups (group A: 8.7 ± 11.1 Torr; group B: 10.8 ± 9.6 Torr).

Hyperemic skin after treatment with nicoboxil/nonivamide Directly after application of the ointment close to the sensor, the tcJ(O_2) decreased to a new steady state (**Fig 4**), whereas the rise of the tcpO_2 indicated an increased hematogenic

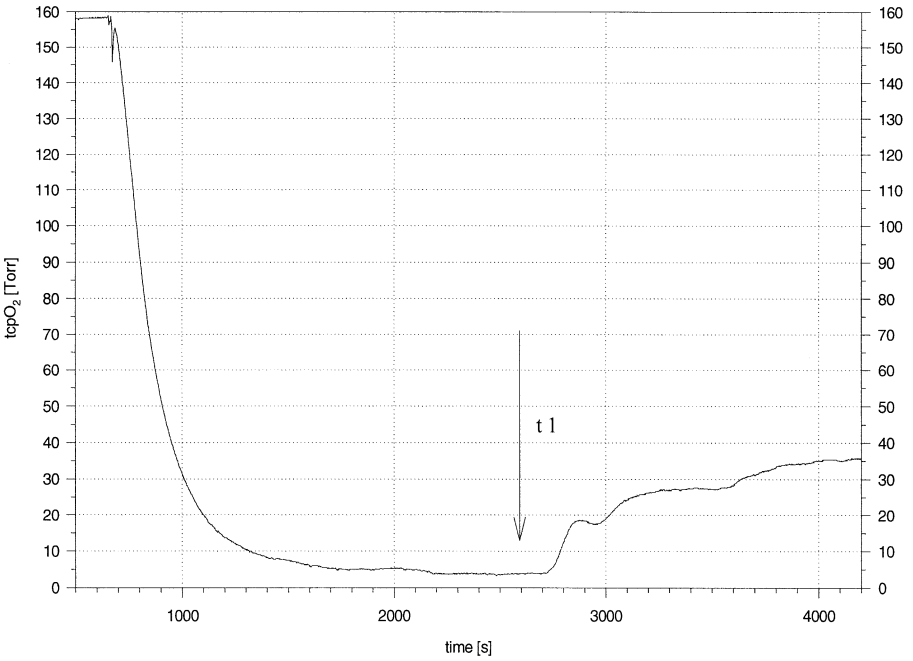

Figure 5. Increase of the $tcpO_2$ after application of a hyperemizing ointment. $tcpO_2$ (37°C) under the influence of nonivamide and nicoboxil ointment, corresponding to **Fig 4**. Application of the sensor on to the skin at 700 s. Marked increase of the $tcpO_2$ after application of the ointment at t1.

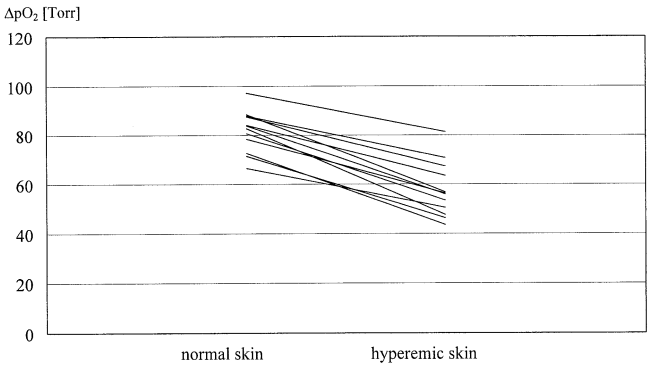

Figure 6. Decrease of the $tcJ(O_2)$ under the influence of nonivamide and nicoboxil in all experiments. $tcJ(O_2)$ (33°C) before and during application of hyperemizing ointment, measured as ΔpO_2.

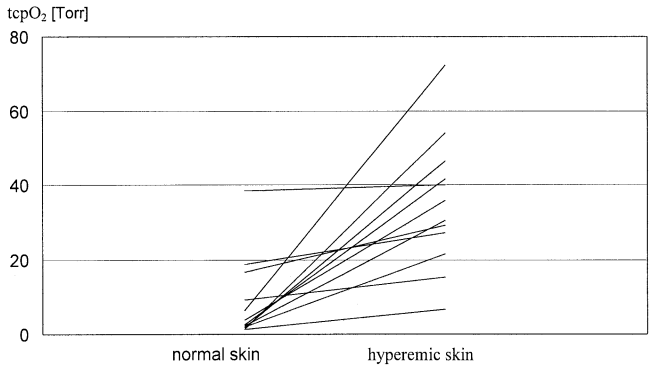

Figure 7. Increase of the $tcpO_2$ in all experiments after hyperemizing the skin. $tcpO_2$ (37°C) before and during application of hyperemizing ointment.

O_2 transport (**Fig 5**). Under the influence of nicoboxil/nonivamide ointment (group A, **Table I**), the $tcJ(O_2)$ decreased from a mean ΔpO_2 of 81.8 ± 8.5 Torr to 57.7 ± 11.1 Torr ($p \leqslant 0.0001$) (**Fig 6**). At the same time, the sensor placed on to the untreated skin in the reference area did not show any significant variations (**Fig 3**): the ΔpO_2 was 77.4 ± 10.6 Torr before and 78.6 ± 10.3 Torr after application of the ointment. In the hyperemic skin, the $tcpO_2$ increased from 8.7 ± 11.1 to 35.1 ± 17.7 Torr ($p = 0.0003$) (**Fig 7**).

Stop of the cutaneous blood flow In all experiments on volunteers of group B (**Table II**), a suprasystolic occlusion resulted in a rise of the $tcJ(O_2)$ at the measuring site 10 cm proximal to the medial malleolus (**Fig 8**). The ΔpO_2 increased from a resting value of 72.8 ± 12.3 Torr to 79.2 ± 12.3 Torr ($p \leqslant 0.0001$). In nine of 20 cases the ΔpO_2 fell below the resting value after discontinuing occlusion. On average, it took 215.9 ± 72.6 s to reach this postocclusive minimum.

During suprasystolic occlusion the mean laser Doppler flow (**Fig 9**) decreased from 22.1 ± 7.0 AU at rest to 13.5 ± 3.3 AU ($p \leqslant 0.0001$). In all experiments the mean laser Doppler flow increased again to a value above the resting value after discontinuing the occlusion [within 11.5 ± 8.3 s to a maximum of 60.3 ± 26.3 AU; ($p \leqslant 0.0001$)]. During occlusion the $tcpO_2$ (**Fig 10**) decreased from a mean value of 10.8 ± 9.6 Torr to 2.1 ± 2.1 Torr ($p \leqslant 0.0001$). After discontinuing the suprasystolic occlusion a rise of the $tcpO_2$ above the resting values was observed in all cases ($p \leqslant 0.0001$). This maximum of 24.1 ± 9.1 Torr was reached within 155.7 ± 21.9 s.

DISCUSSION

The O_2 flux optode is an appropriate tool to measure $tcJ(O_2)$ The described tests revealed that the stability of the O_2 flux optode is suitable to monitor the transcutaneous O_2 uptake. Under laboratory conditions, an almost perfect reproducibility was observed during a time span of 9 h. Application of the optodes on to the skin resulted in greater deviations. But with a maximum discrepancy of 5 Torr between the calculated values of the atmospheric pO_2 before application and after removal, errors due to shifts of the sensitivity of the optode were well below 10%.

At equilibrium, the skin surface pO_2 was reduced by 81.8 ± 8.2 Torr (group A) and by 72.8 ± 12.3 Torr (group B). Under these conditions a marked O_2 flux into the skin was observed which compensated for changes of the hematogenic O_2 transport. Although quantitatively different results might be obtained under normobaric conditions, the set-up allows to study the relationship between the external and the hematogenic O_2 supply of the skin. The measurements at different localizations indicated that regional differences must be taken into account.

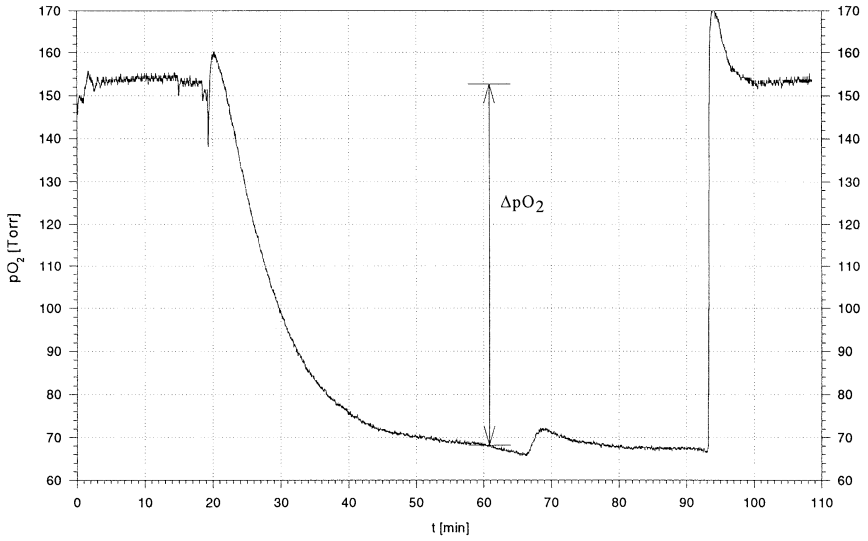

Figure 8. Increase of the tcJ(O_2) during suprasystolic occlusion. tcJ(O_2) measurement (33°C) on the medial lower leg of a healthy volunteer, 10 cm proximal to the medial malleolus. After application of the sensor on to the skin surface (t = 20 min) the skin surface pO_2 decreased and reached a steady state (t = 60 min, ΔpO_2 = 86 - Torr). Ninety percent of the final ΔpO_2 are reached 17 min after fixing the optode on to the skin. During the 61st and 66th min a suprasystolic arterial occlusion was performed (increase of ΔpO_2 to 89 Torr) followed by a reactive hyperaemia (decrease of ΔpO_2 to a minimum of 82 Torr between the 67th and 74th min). The atmospheric pO_2 values determined before application and after removal of the optode were 154.0 Torr and 153.6 Torr.

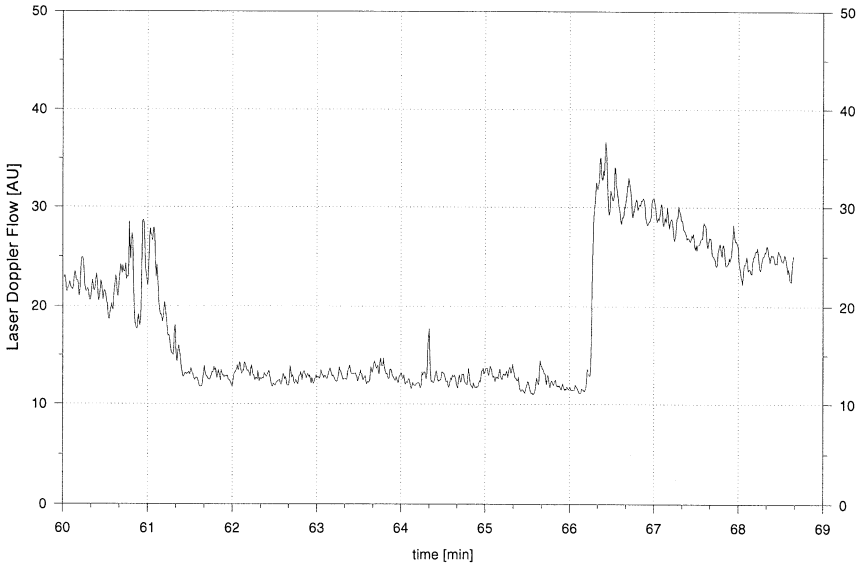

Figure 9. Laser Doppler flow during suprasystolic occlusion. Laser Doppler flow corresponding to **Fig 8**. Marked decrease of the signal during suprasystolic occlusion from 23.1 ± 3.1 AU to 12.0 ± 1.2 AU (biologic zero). The reactive hyperemia reached its maximum of 37.2 AU 17 s after opening the cuff.

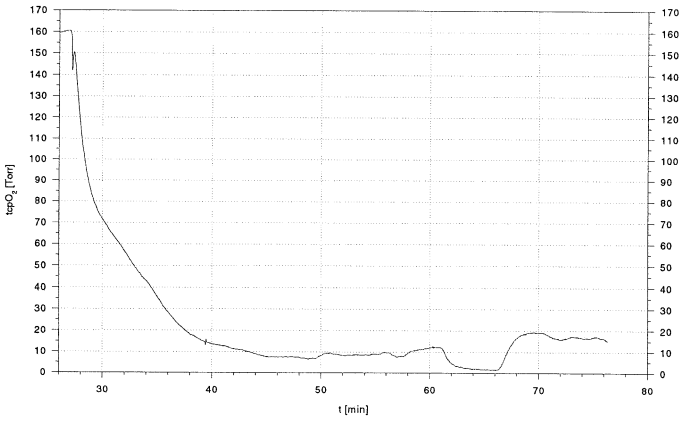

Figure 10. Marked decrease of the $tcpO_2$ during suprasystolic occlusion. $tcpO_2$ at 37°C, corresponding to **Fig 8**. The $tcpO_2$ sensor was mounted at t = 26 min. During suprasystolic arterial occlusion $tcpO_2$ decreased from 12 to 2 Torr.

In hyperemic skin the increased hematogenic O_2 supply was paralleled by a reduced tcJ(O_2) Application of the nonivamide/nicoboxil ointment leads to a depolarization of polymodal C fibers (Fusco and Giacovazzo, 1977). Transmitted by the axon reflex, the effect of the ointment spreads far beyond the application area: Within 12 min after application of 0.02 ml of the nonivamide/nicoboxil compound on to a circular skin area of the lower back with a diameter of 1.2 cm (1.1 cm^2), hyperemia was observed in 13.1 ± 7.3 cm^2. The mean laser Doppler perfusion of all hyperperfused measurement points (4.91 ± 1.60 AU) was only moderately exceeded in the application area (6.10 ± 2.24 AU) (Stücker *et al*, 1998). As a consequence, the use of the nonivamide/nicoboxil close to the O_2 sensors can be regarded as an effective procedure to hyperemize the skin without any alterations of the diffusion properties in the measuring area by the ointment itself. The hyperemizing effect was confirmed by a distinct increase of the $tcpO_2$ from 8.7 ± 11.1 Torr to 35.1 ± 17.7 Torr. tcJ(O_2) decreased markedly, on average by 29%. These *in vivo* findings correlate with computer simulations using a so-called capillary loop model. With this model the balance between the O_2 supply by blood flow and by atmospheric O_2 has been predicted earlier (Lübbers and Grossmann, 1983; Lübbers, 1994). As a consequence of the greater arterial O_2 supply, the pO_2 in the upper dermis increased.

Consecutively, the difference between the pO_2 at the surface of the skin and the subepidermal pO_2 decreased and led to a lesser pO_2 gradient, resulting in a reduced $tcJ(O_2)$.

Stopping the cutaneous blood flow increased the $tcJ(O_2)$ The effects of a reduced skin perfusion were examined by suprasystolic occlusion. This maneuver is a standard test for the assessment of the cutaneous microcirculation (Bircher *et al*, 1994).

Corresponding to the decrease of the $tcJ(O_2)$ in hyperemized skin, a stop of skin perfusion by suprasystolic occlusion resulted in an increased $tcJ(O_2)$, but the change was moderate. Whereas the $tcJ(O_2)$ decreased on average by about 29% in hyperemic skin, an increase of only 9% was observed during a suprasystolic occlusion.

Even if one assumes that the skin surface pO_2 is not yet in equilibrium with the changes in deeper skin layers after a 5 min suprasystolic occlusion (see **Fig 8**), comparison with the time course of the skin surface pO_2 after inducing a hyperemia (**Fig 4**) proves that a stop of skin perfusion has a minor effect on the $tcJ(O_2)$.

Because the $tcJ(O_2)$ is determined by the pO_2 gradients in the upper skin layers, the pO_2 profile in this volume is influenced only weakly by a stop of skin perfusion. These findings correspond with the measurements of the $tcpO_2$. To assess the nutritive blood perfusion, the $tcpO_2$ was recorded at an elevated skin temperature of 37°C resulting in a thermal hyperemia. Even under these conditions the $tcpO_2$ remained low (10.8 ± 9.6 Torr at rest). At normal skin temperature, a $tcpO_2$ close to 0 Torr has been reported (Evans and Naylor, 1967). Therefore, under normal conditions a hematogenic O_2 flux into the upper skin layers can be ruled out. In contrast, a pharmacologically induced hyperemia resulted in a considerable increase of the $tcpO_2$ by a factor of 4.

These findings indicate that in normal, nonhyperemized skin the transcutaneous O_2 uptake from the atmosphere represents the main contribution to the O_2 supply of the upper layers whereas the capillary transport plays a minor part. The balance between the hematogenic O_2 transport and the $tcJ(O_2)$ varies, in hyperemic skin it is shifted towards the capillary O_2 supply.

The epidermal O_2 uptake from the atmosphere is in balance with the capillary O_2 supply Our experiments demonstrate that the cutaneous O_2 uptake is a physiologic process which interferes with the hematogenic O_2 transport. The work of Baumgärtl *et al* (1987; **Fig 1**) might lead to an underestimation of its contribution to the O_2 supply of the skin. Besides the low skin surface pO_2 a hyperemia induced by the puncture of the skin probably resulted in a reduced $tcJ(O_2)$ and as a consequence in a pO_2 minimum unphysiologically close to the skin surface. But even under these experimental conditions it was proved that the O_2 consumption of the epidermis and partly of the deeper skin tissue is fully covered by the $tcJ(O_2)$.

A theoretical analysis with the capillary loop model revealed the main parameters determining the balance between atmospheric and capillary O_2 supply: the structure of the skin, the cutaneous O_2 conductivity, the consumption of O_2 and the cutaneous blood flow (Lübbers and Grossmann, 1983; Lübbers, 1994). During our experiments the skin structure remained unchanged. The O_2 conductivity of the stratum corneum is strongly dependent on the skin humidity (Huch *et al*, 1981). To standardize the measurements in this study, the skin was artificially humidified. The activity of mitochondria is reported to be constant over a wide pO_2 range (Wilson *et al*, 1979); greater changes of the O_2 consumption seem unlikely under our conditions. Therefore, the changes of the $tcJ(O_2)$ described in this study are mainly due to the variations of the cutaneous blood flow.

Clinical relevance The examination of the role of the $tcJ(O_2)$ in skin physiology has clinical relevance: Air-tight covering of the skin is an important therapeutic principle in the treatment of open wounds and of chronic stationary psoriasis. Whereas various models regarding the occlusive effect in wound healing have been published, hypotheses concerning the treatment of stationary psoriasis are missing. The positive effect on wound healing is well described. One explanation is the special microenvironment created through retention of moisture and soluble factors such as growth factors and enzymes (Chen *et al*, 1992). Additionally, the occlusion-induced reduction of the pO_2 might play an independent part in the process of healing. An increased angiogenesis due to the restricted O_2 supply seems plausible. In psoriasis plaques the diameter of the blood vessels and the cutaneous blood flow are already increased to supply the metabolically active, hyperplastic epidermis (Braverman and Sibley, 1982; Auer *et al*, 1994). Possibly the capillary O_2 transport does not suffice to compensate for the missing $tcJ(O_2)$ in occluded psoriatic skin. This O_2 deficit might be the reason for the normalization of the epidermal mitotic activity and thickness. We believe that this hypothesis should be examined further.

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